

Case report

Serial proton spectroscopy in a case of adult-onset subacute sclerosing panencephalitis

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Received 28 August 2003; received in revised form 22 December 2004; accepted 5 January 2005

Abstract

A case of subacute sclerosing panencephalitis in a 27-year-old man was serially evaluated with proton magnetic resonance spectroscopy. Metabolic abnormalities included decreased *N*-acetylaspartate and elevated choline and *myo*-inositol in a lesion visible on magnetic resonance imaging and in normal-appearing white matter. Lactate appeared increased within the lesion. Metabolic impairment was persistent after intrathecal interferon- α treatment. Spectroscopy pointing to ongoing inflammation, gliosis, and possible membrane turnover was more sensitive than imaging in detecting widespread pathology within the white matter.

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Keywords: Electroconvulsive therapy; Interferon- α ; Proton magnetic resonance spectroscopy; Psychosis; Subacute sclerosing panencephalitis

1. Introduction

Subacute sclerosing panencephalitis (SSPE) is an inflammatory, chronic-progredient encephalopathy caused by an autoimmune process against persistent measles virus in the central nervous system. Typically,

it occurs during childhood, presenting with neurological symptoms, and, less frequently, in early adulthood. In rare cases, psychotic symptoms may be the first manifestation of illness, making diagnosis difficult (Singer et al., 1997). Effective therapy is still not available. Some reports suggest that experimental treatment with interferon- α may delay progression of the inflammatory process (Gokcil et al., 1999). A non-invasive means to assess the therapeutic efficiency on a quantitative basis is warranted. Proton magnetic resonance spectroscopy (MRS) was recently shown

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to be capable of detecting severe metabolic abnormalities associated with inflammatory processes (Salvan et al., 1999). Here, we report on a nearly 2-year follow-up in an unusual case of adult-onset SSPE, in which encephalitis and interferon treatment were monitored by absolute concentrations of cerebral metabolites measured by ^1H MRS.

2. Case report

The first symptoms of our male patient appeared in June at the age of 27 years; relatives noted abnormal behavior: the patient was unusually anxious and distraught. In July, a first epileptic seizure occurred. Magnetic resonance imaging (MRI) of the brain was normal at that time, and an electroencephalogram (EEG) revealed focal slowing. In August, delusions, increased anxiety and disorganized speech led to treatment with risperidone, 6 mg/day. Shortly thereafter, the patient experienced a second fit. Cerebrospinal fluid (CSF) showed oligoclonal bands. After improvement of the psychotic symptoms, he wished to taper risperidone. In November, anxiety and restlessness increased, the patient's speech was disorganized, and he developed the delusion of being influenced. He was admitted to the hospital, and haloperidol, 30 mg, was initiated. Two weeks later, he developed a malignant neuroleptic syndrome with increased temperature and elevated creatine phosphokinase. Haloperidol had to be discontinued, and the treatment was continued on an intensive care unit. In December, he developed a catatonic state with immobility, catalepsy, echolalia, and later, mutism, and was referred to the university hospital for electroconvulsive therapy (ECT). After a series of 10 treatments, the organic catatonic syndrome disappeared, but delusions, hallucinations, and disorganized speech reappeared. Three further ECT sessions did not improve the clinical symptoms. The neurological examination showed a slight left-sided rigor, beginning aphasia, and memory impairment. The EEG displayed triphasic complexes, and the diagnosis of SSPE was confirmed by detecting a considerable increase of specific antimeasles antibodies in serum and CSF. Written informed consent was obtained from the patient's father and sister to perform MRS after diagnostic MRI. Afterwards, he was treated with intrathecal interferon- α , 1.5 million IU for 30

days via a neurosurgically implanted Rickham reservoir. This treatment was complicated at the end by a meningoencephalitis with severe delirium. One year after onset of illness, he recovered and exhibited organic psychic syndrome, slight aphasia, memory disturbances, and sometimes depressed mood. At this time (4 months after the first MRS), a second MRS was performed. Over the following 10 months, his state remained stable, and the last MRS was performed.

2.1. Serial MRI/MRS: methods and results

A 1.5-T system (Magnetom 63SP, Siemens, Erlangen, Germany) with a circularly polarized head coil was used for MRI/MRS. Imaging included transverse proton-density (PD) and T_2 -weighted (TR 2500 ms; TE 15/90 ms) and coronal T_1 -weighted (TR 644 ms; TE 15 ms) spin-echo sequences (FOV 230 mm; slice thickness 6 mm). T_2 -weighted images showed diffuse white matter (WM) lesions quite symmetrically within the occipital WM. The U-fibers, as well as the deep WM, were involved (Fig. 1a). No significant PD changes were found. T_1 -weighted images showed definite lesions, which appeared smaller than on T_2 -weighted images; hence, the T_1 lesions were located in the core of the T_2 lesions. There was no mass effect and no apparent cortical involvement. A control examination after 1 month showed no progression. However, with progressive clinical deterioration, a corresponding progression of MRI findings occurred after 4 months in both frontal lobes, with severe changes, especially on the left.

Proton spectra were acquired applying the STEAM (Frahm et al., 1990) technique (stimulated echo acquisition mode; TR 3 s; TE 20 ms; 128–200 acquisitions) as outlined previously (Möller et al., 2002). One cubic volume of interest (VOI 3.4 ml) was centered in a T_2 lesion in the left occipital WM involving both deep and subcortical WM (Fig. 1a). A second spectrum from normal-appearing white matter (NAWM) was recorded from a 4.5-mL VOI in the right frontoparietal WM (Fig. 1c). Quantification to obtain absolute metabolite concentrations was performed by LCModel (Provencher, 1993) using tissue water as internal reference. Results were compared to spectra from normal WM in 14 healthy volunteers (9 males, 5 females, age 24.0 ± 2.4 years). Patient data were

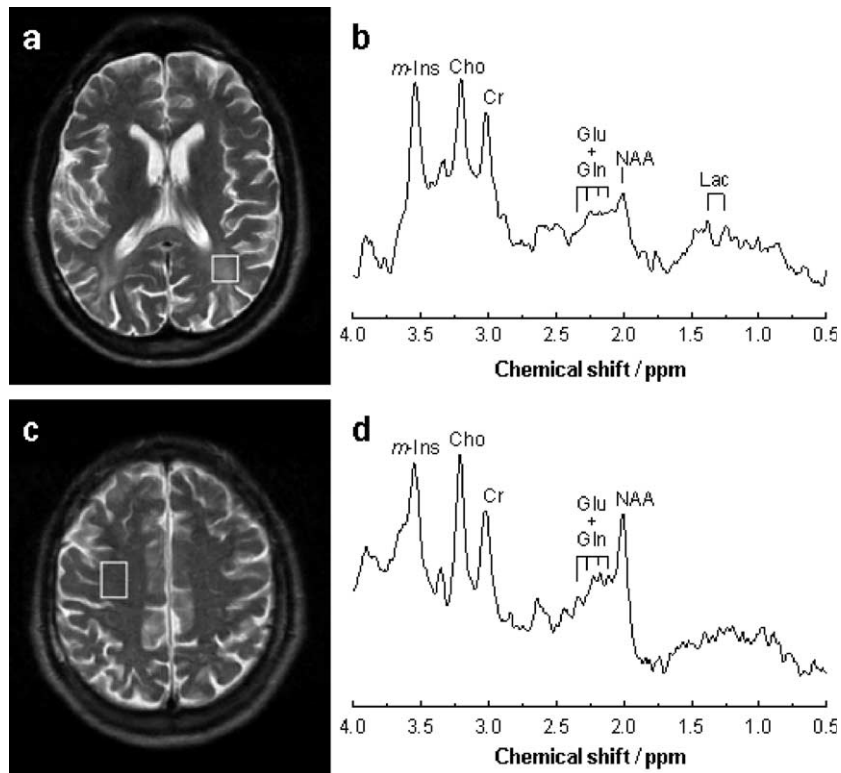


Fig. 1. T_2 -weighted images and results of the first ^1H MRS examination (i.e., pretreatment). Boxes indicate VOIs selected for spectroscopy. (a) Hyperintense lesion with abnormal T_2 prolongation in the left occipital WM (VOI 1). (b) Corresponding spectrum of VOI 1. (c) Normal-appearing right fronto-parietal WM (VOI 2). (d) ^1H MRS result from VOI 2.

regarded as significantly abnormal (one-sided test) on the 5%, 1%, or 0.1% level if they exceeded the mean control value by more than 1.65, 2.33, or 3.08 standard deviations (SD).

2.1.1. Nine months after onset of symptom

The spectrum recorded from the WM lesion (VOI 1) on the first admission (Fig. 1b) indicates substantial reduction of *N*-acetylaspartate (NAA) to 37% of the mean control level, elevated choline compounds (Cho) at 169% of normal, and dramatically increased *myo*-inositol (*m*-Ins; 345% of normal). Concentrations are summarized in Table 1. In the NAWM (VOI 2), qualitatively similar but less pronounced changes (NAA at 69%, Cho at 166%, *m*-Ins at 230% of normal) were observed (Fig. 1d). Lactate (Lac) was well above 1 mM and, hence, abnormally high in the lesion, whereas its concentration in NAWM was not significantly different from values.

2.1.2. Thirteen months after onset of symptom

Reexamination of both regions after 4 months (i.e., 13 months after onset of symptoms) demonstrated persistent metabolic impairment with reduced NAA and elevated Cho and *m*-Ins (at 35%, 150%, and 315% of normal, respectively) in the lesion as well as in NAWM (at 61%, 158%, and 248% of normal, respectively). A further abnormality in the lesion was now a reduction in the signal areas from glutamate (Glu) and glutamine (Gln). The sum of the two concentrations (60% of normal) is given in Table 1. Inspection of the individual contributions from both compounds, which are fitted with less accuracy due to the strong signal overlap at 1.5 T, indicated that this decline almost entirely resulted from a loss of Glu. At this time, a third spectrum (VOI 3; 3.4 ml) was recorded from a new lesion in the right parietal WM and yielded consistent abnormalities (Lac: 1.47 mM, NAA: 3.51 mM, Glu+Gln: 5.74 mM, total creatine:

Table 1

Absolute metabolite concentrations (in mM) in a white-matter (WM) lesion and normal-appearing white matter (NAWM) in a patient with SSPE and corresponding results from normal white matter (NWM) of healthy controls (mean value \pm standard deviation)

Metabolite ^a	SSPE patient						Control data
	WM lesion			NAWM			NWM
	After 9 months	After 13 months	After 20 months	After 9 months	After 13 months	After 20 months	(<i>n</i> = 14)
Lac	3.00***	0.35	2.97***	1.20	1.31	–	<1.0
NAA	4.13***	3.90***	0.41***	7.64***	6.74***	5.30***	11.14 \pm 0.60
Glu + Gln	10.73	6.21*	4.00**	11.13	11.56	12.74	10.33 \pm 2.22
tCr	6.30	6.89	4.20*	6.54	7.69	5.64	5.81 \pm 0.71
Cho	2.88***	2.55**	2.08	2.82***	2.68***	3.08***	1.70 \pm 0.34
<i>m</i> -Ins	14.57***	13.31***	10.08***	9.71***	10.48***	6.82***	4.22 \pm 0.74

* P < 0.05; ** P < 0.01; *** P < 0.001.

^a Cho=choline compounds, Gln=glutamine, Glu=glutamate, Lac=lactate; *m*-Ins=*myo*-inositol, NAA=*N*-acetylaspartate, tCr=total creatine.

5.03 mM, Cho: 2.51 mM, *m*-Ins: 8.41 mM) as compared with VOI 1.

2.1.3. Twenty months after onset of symptoms

Trends were unchanged 20 months after onset of symptoms, with extremely low NAA, further reduction of Glu + Gln, and elevated *m*-Ins in the lesion (VOI 1; 4%, 39%, and 239% of normal, respectively) and reduced NAA, elevated Cho, and elevated *m*-Ins in NAWM (VOI 2; 48%, 181%, and 162% of normal, respectively). Additionally, a decrease in the total creatine (tCr; i.e., creatine plus phosphocreatine) concentration was now observed in the lesion (72% of normal).

3. Discussion

Extending previous qualitative work in selected cases (Alkan et al., 2003, 2004; Cakmakci et al., 2004; Kato et al., 2002; Salvan et al., 1999; Takashima et al., 2003), the present longitudinal study reveals a metabolic profile, which reflects a variety of neuropathological processes, including inflammation, gliosis, and potentially membrane turnover. Severe disturbances are not only manifested in lesions visible to MRI but also in the NAWM thus underlining the diffuse nature of the disease.

An increase in Cho towards normal levels and otherwise stable metabolite concentrations were previously found after electroconvulsive therapy (ECT) in depressive patients (Ende et al., 2000). As this cannot explain any of the metabolic abnormalities in

our study, we may rule out a relevant influence of ECT in our data.

N-acetylaspartate is largely (if not entirely) present in neuronal cells, and its reduction in lesions and NAWM is a sensitive sign of neuronal damage extending from transient axonal impairment to irreversible cell loss (Miller, 1991). In a previous study, an increased NAA/Cr ratio was reported in a 22-year-old woman with adult-onset SSPE after 6 months of treatment with intraventricular interferon- β and oral inosine pranobex, and attributed to therapeutic response (Takashima et al., 2003). In our patient, the progressive decline of NAA found in all VOIs indicates progression of damage. This assumption is further supported by the accompanying decrease of Glu in the lesion at the second and third examinations, whereas no indication of a reduction of Gln contained in the glia was found. This underlines the advantage of quantitative MRS yielding absolute metabolite concentrations to be used as unambiguous markers for assessing potential treatment effects.

From studies in cultured cells, there is evidence that *m*-Ins is preferentially located in glial cells (Brand et al., 1993), although it remains uncertain to what extent it is a specific astrocyte marker (Fisher et al., 2002). We may speculate that the dramatic elevation in lesions and NAWM associated with SSPE accompanies the pathology of astrocytic proliferation and gliosis. We cannot exclude that the parallel increase in the concentrations of *m*-Ins and Cho additionally points to myelin breakdown with release of both compounds from immobile and therefore MRS-invisible membrane constituents. However, since Cho

showed similar concentrations in the lesion and the NAWM without marked regional heterogeneity, its rise predominantly reflects inflammatory disorder rather than demyelination. Focal elevation of lactate in the lesion is presumably related to macrophagic infiltration. The reduced tCr concentration in the WM lesion 20 months after onset of symptoms is indicative of segmental necrosis. This also explains the regression in the elevations of Cho and *m*-Ins, which is, hence, no indicator of metabolic improvement. By contrast, despite clinical stabilization at that time, metabolic disturbances persisted without signs of normalization. Note that absolute quantitation of metabolite concentrations was necessary for the unequivocal detection of such abnormalities, whereas commonly used metabolite ratios relative to tCr would produce ambiguous results as metabolite ratios were instable over the course of the disease.

Proton MRS was more sensitive than MRI in detecting widespread pathology occurring in the NAWM in line with the diffuse nature of the disease. Although the results are not diagnostically specific, sensitive markers of pathologies typically found in SSPE are obtained. Hence, quantitative follow-up studies permitting non-invasive monitoring of metabolic disturbances provide useful markers of ongoing neuropathological processes.

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